UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/994,468	12/19/97	LYMAN S	

HM22/0523

LAW DEPARTMENT
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KERR, EXAMINER

ART UNIT	PAPER NUMBER

DATE MAILED: 05/23/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Offic Action Summary	Application No. 08/994,468	Applicant(s) LYMAN ET AL.	
	Examiner Janet Kerr	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

Response to Amendment

Applicant's amendment, filed 11/20/00 has been entered in part. The request to cancel text following "December 7, 1993, now abandoned" on page 1, line 15 of the specification has not been entered as this date does not appear on line 15.

Claims 1-30 remain pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (newly applied).

Claims 8 and 16 are directed to a medium comprising cell growth media, flt3-ligand and IL-6. However, the specification does not disclose, nor do the claims as originally filed, recite a media composition comprising IL-6. Applicants are required to cancel the claims or amend the claims such that the claimed invention is supported by the disclosure in the instant application.

This is a new matter rejection.

Claims 1-8, 17-26, 29 and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (newly applied).

The claims are directed to hematopoietic cell expansion media comprising flt3-ligand (flt3-L), or comprising a soluble polypeptide that comprises an amino acid sequence that is at least 80% identical to the amino acids 28-160 of SEQ ID NO: 6.

While the specification adequately describes mouse and human flt3-L, and a soluble polypeptide that comprises amino acids 28-160 of SEQ ID NO: 6, the specification fails to provide sequence data for the broadly claimed flt3-L (i.e., sequence data from species other than those disclosed in the instant application) or soluble peptides that comprise amino acid sequences that are at least 80% (and less than 100%) identical to the amino acids 28-160 of SEQ ID NO: 6 such that the altered sequence retains its solubility, the ability to bind to the flt3 receptor on hematopoietic cells and stimulate proliferation (expansion) of the cells. In addition, the specification does not disclose which particular amino acid(s) can be altered (i.e., deleted, substituted, or added, or a combination thereof) to obtain a sequence which is less than 100% identical to that of amino acids 28-160 of SEQ ID NO: 6 such that the altered sequence retains its solubility, the ability to bind to the flt3 receptor on hematopoietic cells and stimulate proliferation (expansion) of the cells. As there is no disclosure of flt3-L sequences other than mouse and human, and as there is no disclosure of any soluble peptides other than that of amino acids 28-160 of SEQ ID NO: 6, the specification does not provide an adequate written description for the polypeptides instantly contemplated having less than 100% identity.

The disclosure does not provide a written description that would allow one of skill in the art to immediately envisage the specific structure for any non-disclosed polypeptide. While applicants were obviously in possession of the mouse and human flt3-L polypeptide and soluble polypeptide obtained from the disclosed SEQ ID NO: 6, the specification provides no information regarding the broadly claimed flt3-L and soluble polypeptides. The limited information provided in the specification is not deemed sufficient to reasonably convey to one skilled in the art that applicants were in possession of polypeptides besides the disclosed SEQ ID NOS., at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

The instant application does not provide a written description that would allow one of skill in the art to immediately envisage the specific structure for the flt3-L polypeptides from species other than mouse and human or for soluble polypeptides having less than 100% identity to amino acids 28-160 of SEQ ID NO: 6. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

As there is no disclosure of polypeptides having a sequence identity of less than 100%, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The limited information provided in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the broadly claimed polypeptides, at the time the application was filed. Thus it is concluded that the written description provision of 35 U.S.C. §112, first paragraph, is not satisfied for the claimed polypeptides. Applicants are reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-8, 17-26, 29 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for hematopoietic cell expansion media comprising human or mouse flt3-L, or comprising a soluble polypeptide consisting of amino acids 28-160 of SEQ ID NO: 6, does not reasonably provide enablement for hematopoietic cell expansion media

comprising flt3-L from species other than mouse or human, or comprising a soluble polypeptide that comprises an amino acid sequence that is at least 80% identical to the amino acids 28-160 of SEQ ID NO: 6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims are directed to hematopoietic cell expansion media comprising flt3-ligand (flt3-L), or comprising a soluble polypeptide that comprises an amino acid sequence that is at least 80% identical to the amino acids 28-160 of SEQ ID NO: 6.

While the specification is enabling for a medium composition comprising human or mouse flt3-L, or comprising a soluble polypeptide consisting of amino acids 28-160 of SEQ ID NO: 6, the specification is non-enabling for hematopoietic cell expansion media comprising a soluble polypeptide that comprises an amino acid sequence that is at least 80% identical to the amino acids 28-160 of SEQ ID NO: 6, or comprising flt3-L from species other than mouse or human. The specification only discloses mouse and human flt3-L, and a soluble flt3-ligand which consists of the amino acids 28-160 of SEQ ID NO: 6. There is no guidance in the specification as to how to determine the structures of flt3-L from species other than mouse or human. In addition, there is no guidance in the specification as to how to make a soluble polypeptide which comprises an amino acid sequence that is at least 80% identical to the amino acids 28-160 of SEQ ID NO: 6 such that the polypeptide can bind to its putative receptor. For example, the specification does not disclose which amino acids can be substituted, deleted or inserted, or how to make particular combinations of substituted, deleted, or inserted amino acids such that the polypeptide will retain its solubility characteristic and the ability to bind to its putative receptor. Moreover, a sequence search of the prior art and patent literature did not reveal any amino acid sequences of flt3-L having at least 80% identity to the amino acids 28-160 of SEQ ID NO: 6. It should also be noted that the skilled artisan cannot predict, *a priori*, functional activity of particular amino acid sequences based on primary amino acid structure; structure/function relationships need to be determined empirically (see, e.g., Rudinger, in Peptide Hormones, 1976, page 6) as too little is

known about protein folding and as an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone has not been described (see, e.g., Ngo *et al.*, in The Protein Folding Problem and Tertiary Structure Prediction, eds. Merz, Jr. and Le Grand, Birkhauser, Boston, pages 491-495, 1994, see page 492, left column, first paragraph under "Future Work"). Moreover, making and testing all of the possible soluble peptides encompassed in the claimed invention for those that are soluble, and bind to the flt3 receptor such that they are capable of stimulating hematopoietic cell proliferation would require undue experimentation. For example, using the formula

$$\frac{X^n L^n}{n!}$$

Which is an approximation of the formula:

$$\sum_{i=1}^{n} = X^n L \frac{(L-1)(L-2)\ldots(L-n)}{n!}$$

where n= # of residues inserted, deleted, or substituted,

L= length of the polymer, and

x= # of different monomers for one location,

the number of possible amino acid sequences having 80% identity to amino acids 28-160 of SEQ ID NO: 6 which are generated from <u>just substitutions alone</u> is estimated to be $7x10^{61}$ sequences (in the instant case, x=19 different amino acids which can be substituted at amino acid position 28 through 160, L= the specified 133 amino acids of SEQ ID NO: 6, i.e., 133 is the number of amino acids in the polypeptide spanning amino acid number 28 through amino acid number 160, and n=26 (20% of the 133 amino acids are substituted to arrive at a sequence having 80% identity

over the 133 amino acids). This calculation does not take into consideration the number of possible amino acid sequences one can additionally generate from mere deletions, or from mere insertions, or from combinations of substitutions, deletions, or insertions of amino acids, to arrive at amino acid sequences having 80% identity to amino acids 28-160 of SEQ ID NO: 6.

Given the vast number of polypeptides encompassed in the claimed invention, it would require undue experimentation for the skilled artisan to make the claimed polypeptides and test the claimed polypeptides to determine which polypeptides having 80% identity to amino acids 28-160 of SEQ ID NO: 6 retain the biological properties required for expansion of hematopoietic cells. One of skill in the art could not make or use the claimed expansion media without undue experimentation.

Applicant's arguments filed 11/20/00 have been fully considered but they are not persuasive.

It is argued that (1) one skilled in the art could, without undue experimentation, identify flt3-L polypeptides that are at least 80% identical to a native flt3-L amino acid sequence and which bind flt3, that (2) it is not necessary than an applicant disclose all the embodiments of his invention (citing *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976) as support), and that (3) the specification discloses suitable binding assay procedures to test for the ability of the flt3-L variant to bind to the flt3 receptor. Applicants rely on *Ex parte Mark*, 12 USPQ 2d 1904, to argue that generation and testing of variant flt3-L polypeptides that are at least 80% identical to amino acids 28-160 of SEQ ID NO: 6 requires no more than routine experimentation.

These arguments are not persuasive. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).2164.01(a). The specification lacks guidance as to which amino acids to substitute, delete, or insert to arrive at variant flt3-L polypeptides that are at least 80% identical to amino acids 28-160 of SEQ ID NO: 6 which are soluble, which bind to the flt3 receptor, and which stimulate proliferation of hematopoietic cells. Moreover, as indicated in the above rejection, at a minimum (i.e., just based on substitutions

alone), $7x10^{61}$ variant polypeptides are encompassed in the claimed invention. It would require undue experimentation, not routine experimentation, to make and test a minimum of $7x10^{61}$ variant polypeptides to practice the claimed invention. With respect to *Ex parte Mark*, while one of ordinary skill in the art could routinely determine whether deletion or replacement of specified residues would result in a mutein encompassed by the claimed invention, this fact situation is quite distinct from the instant invention. There is no recitation in the claims or disclosed in the specification, of a specific residue to delete or replace. As stated above, the claims encompass a minimum of $7x10^{61}$ variant polypeptides. Given that the specification does not disclose any variant polypeptide, it would require undue experimentation to make and test a minimum of $7x10^{61}$ variant polypeptides.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-9, 11-18 and 27-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 3-8 are rendered vague and indefinite by the phrase "A hematopoietic cell expansion media" as it is unclear if applicants are claiming one medium in using the singular "A", or if applicants are claiming more than one medium in using the plural "media". The claim is also rendered vague and indefinite by the phrase "cell growth media" as it is unclear if multiple medium formulations are included in the "hematopoietic cell expansion media".

Claims 1 and 2 are rendered vague and indefinite by the abbreviation "flt3-L". It is suggested that applicants amend the claims to either delete "flt3-L" and insert "flt3-ligand" or to

place flt3-L in parentheses (flt3-L) and insert prior to the parenthetical expression the term flt3-ligand.

Claims 9, and 11-16 are rendered vague and indefinite by the phrase "comprising a recombinant human flt3-ligand" as it is unclear if the recombinant human flt3-ligand is added in addition to the flt3-ligand recited in the claims upon which claims 9 and 11-16 depend or if the recombinant human flt3-ligand is further defining the flt3-ligand recited in the claims upon which claims 9 and 11-16 depend.

Claims 17 and 18 are rendered vague and indefinite as it is unclear if the hematopoietic cell expansion caused by the sufficient amount of the cellular growth factor is independent of the cell expansion caused by the flt3-ligand as recited in claims 1 and 2, i.e., does the "sufficient amount of cellular growth factor" cause cell expansion in the absence of flt3-ligand?

Claims 19 and 20 are rendered vague and indefinite by the phrase "wherein the flt3-ligand" as there is no "flt3-ligand" recited in the claims upon which claims 19 and 20 depend. It is suggested that applicants amend claims 1 and 2 by deleting "flt3-L" and inserting "flt3-ligand" to overcome this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2, 5, 17, and 18 are rejected under 35 U.S.C. 102(a) as being anticipated by Lyman *et al.* (Cell, 75:1157-1167, December 17,1993, of record).

Lyman *et al.* teach a hematopoietic stem cell expansion medium comprising cell growth media, flt3-ligand, and IL-3 or steel factor, in amounts sufficient to cause hematopoietic cell expansion, and a method of expanding hematopoietic cells using the medium (see, e.g., page 1165, under the section entitled "Hematopoiesis Assays", and pages 1161-1162, under the section

entitled "Murine flt3 Ligand Stimulates the Proliferation of Human CD34-Positive Bone Marrow Cells).

Thus the hematopoietic stem cell expansion media and method of expanding the cells taught by Lyman *et al.* anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4, 7, 17, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lyman *et al.* (Cell, 75:1157-1167, 1993, of record) taken with Gillis *et al.* (U.S. Patent No. 5,199,942, 4/6/93, effective filing date of 9/26/91, of record).

Lyman *et al.* teach a stem cell expansion medium comprising a cell growth medium, flt3-ligand, and IL-3 or steel factor, in amounts sufficient to cause hematopoietic cell expansion and methods of using the expansion medium to expand hematopoietic cells (see, e.g., page 1165,

under the section entitled "Hematopoiesis Assays", and pages 1161-1162, under the section entitled "Murine flt3 Ligand Stimulates the Proliferation of Human CD34-Positive Bone Marrow Cells).

Lyman *et al.* do not teach a hematopoietic stem cell expansion media comprising the claim-designated factors, GM-CSF, or GM-CSF/IL-3 fusion protein.

However, Gillis teaches a hematopoietic stem cell expansion media comprising cell growth media, autologous serum and a growth factor selected from the group consisting of SF, IL-1, IL-3, GM-CSF, GM-CSF/IL-3 fusion proteins and combinations thereof (see, e.g., column 3, lines 46-52, and columns 7-10, under "Example 1").

It would have been obvious to one of ordinary skill in the art to modify the hematopoietic stem cell expansion media of Lyman *et al.* by substituting SF or IL-3 with GM-CSF or GM-CSF/IL-3 fusion proteins taught by Gillis in view of the teachings of Gillis that these factors, when added to cell culture media, stimulate proliferation of hematopoietic stem cells *in vitro*. As Lyman *et al.* teach a hematopoietic cell expansion medium comprising Flt3-ligand alone or in combination with either SF or IL-3, which stimulates proliferation of hematopoietic cells, and as Gillis teaches a hematopoietic stem cell expansion medium that stimulates proliferation of hematopoietic cells, comprising SF, GM-CSF or GM-CSF/IL-3 fusion proteins, one of ordinary skill in the art would have had a high expectation of successfully substituting factors known in the art to enhance proliferation of hematopoietic stem cells for the purpose of providing a hematopoietic stem cell expansion media comprising Flt3-ligand in combination with any one of SF, IL-3, GM-CSF or GM-CSF/IL-3 fusion proteins, to be utilized in a method of stimulating the proliferation of hematopoietic stem cells barring evidence to the contrary. Taken together, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare a medium formulation comprising flt3-ligand alone or in combination with hematopoietic growth factors such as SF, GM-CSF, or GM-CSF/IL-3 fusion protein, to use in a method of expanding hematopoietic stem cells as media formulations comprising the claim-designated components have been shown to successfully expand hematopoietic stem cells.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Claims 1-4, 8, 17, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lyman *et al.* (Cell, 75:1157-1167, 1993, of record) taken with Heimfeld *et al.* (WO 93/08268, 4/3/93, of record).

Lyman *et al.* teach a stem cell expansion medium comprising a cell growth medium, flt3-ligand, and IL-3 or steel factor, in amounts sufficient to cause hematopoietic cell expansion and methods of using the expansion medium to expand hematopoietic cells (see, e.g., page 1165, under the section entitled "Hematopoiesis Assays", and pages 1161-1162, under the section entitled "Murine flt3 Ligand Stimulates the Proliferation of Human CD34-Positive Bone Marrow Cells).

Lyman *et al.* do not teach a hematopoietic stem cell expansion media comprising the claim-designated factors, GM-CSF, G-CSF or IL-6. However, Heimfeld *et al.* teach a hematopoietic stem cell expansion medium, comprising cell growth media, and a growth factor such as IL-1, IL-3, IL-4, IL-6, IL-7, SCF, GM-CSF, G-CSF, M-CSF, TGF-β, TNF-α, αINF, FGF, PDGF, IGF-1, and IGF-2 (see, e.g., page 5, lines, 14-29).

It would have been obvious to one of ordinary skill in the art to modify the hematopoietic stem cell expansion media of Lyman *et al.* by substituting SF or IL-3 with GM-CSF, G-CSF or IL-6 as taught by Heimfeld *et al.* in view of the teachings of Heimfeld *et al.* that these factors, when added to cell culture media, stimulate proliferation of hematopoietic stem cells *in vitro*. As Lyman *et al.* teach a hematopoietic stem cell expansion medium comprising Flt3-ligand and SF which stimulates proliferation of stem cells, and as Heimfeld *et al.* teach a hematopoietic stem cell expansion medium comprising SF, G-CSF, GM-CSF or IL-6 that stimulates proliferation of stem cells, one of ordinary skill in the art would have had a high expectation of successfully providing a hematopoietic stem cell expansion media comprising Flt3-ligand in combination with any one of

SF, GM-CSF, G-CSF, or IL-6, and utilizing this expansion media to stimulate proliferation of hematopoietic stem cells *in vitro* barring evidence to the contrary. Taken together, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare a media formulation comprising flt3-ligand alone or in combination with hematopoietic growth factors such as SF, GM-CSF, IL-6, G-CSF, or GM-CSF/IL-3 fusion protein, to use in a method of expanding hematopoietic stem cells as media formulations comprising the claim-designated components have been shown to successfully expand hematopoietic cells.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Claims 1, 2, 4, 6, 17, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lyman *et al.* (Cell, 75:1157-1167, 1993, of record) taken with Palsson *et al.* (U.S. Patent No. 5,635,386, 1997, effective filing date of ½/92, newly applied).

Lyman *et al.* teach a stem cell expansion medium comprising a cell growth medium, flt3-ligand, and IL-3 or steel factor, in amounts sufficient to cause hematopoietic cell expansion and methods of using the expansion medium to expand hematopoietic cells (see, e.g., page 1165, under the section entitled "Hematopoiesis Assays", and pages 1161-1162, under the section entitled "Murine flt3 Ligand Stimulates the Proliferation of Human CD34-Positive Bone Marrow Cells).

Lyman *et al.* do not teach a hematopoietic stem cell expansion media comprising the claim-designated factors, GM-CSF, or EPO. However, Palsson *et al.* teach a hematopoietic cell expansion media comprising cell growth media, and a growth factor such as GM-CSF and EPO and a method of increasing productivity of the hematopoietic cells (i.e., expansion) *in vitro* (see, e.g., columns 37-41, Example 2).

It would have been obvious to one of ordinary skill in the art to modify the hematopoietic stem cell expansion media of Lyman *et al.* by substituting SF or IL-3 with GM-CSF, or EPO as

taught by Palsson *et al.* in view of the teachings of Palsson *et al.* that these factors, when added to cell culture media, stimulate proliferation of hematopoietic cells *in vitro*. As Lyman *et al.* teach a hematopoietic stem cell expansion medium comprising Flt3-ligand and SF or IL-3 which stimulates proliferation of hematopoietic cells, and as Palsson *et al.* teach a hematopoietic cell expansion medium comprising GM-CSF or EPO which stimulates proliferation of hematopoietic cells, one of ordinary skill in the art would have had a high expectation of successfully providing a hematopoietic stem cell expansion media comprising Flt3-ligand in combination with any one of GM-CSF, or EPO, and utilizing this expansion media to stimulate proliferation of hematopoietic cells *in vitro* barring evidence to the contrary. Taken together, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare a media formulation comprising flt3-ligand alone or in combination with hematopoietic growth factors such as GM-CSF or EPO, to use in a method of expanding hematopoietic stem cells as media formulations comprising the claim-designated components have been shown to successfully expand hematopoietic stem cells.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Applicant's arguments filed 5/26/00 have been fully considered but they are not persuasive. It is argued that the Lyman *et al.* reference was published in December of 1993 and is not available as prior art and this date is less than one year before the filing of Application No. 08/209,502, filed March 7, 1994, the specification of which fully supports the claimed invention of the instant application (see page 6 of applicants' Response). This argument is not persuasive as the rejection has been made under 35 U.S.C. 102(a). Although the Lyman *et al.* reference was published less than 3 months prior to the March 7, 1994 filing date of Application No. 08/209,502, the reference is appropriately applied as the invention has been described by others,

i.e., there are 16 co-authors for the Lyman *et al.* reference, two of which are the inventors of the instant application.

It is also argued that claims 1 and 2, as amended, and claim 5 are fully supported by the disclosure in the parent Application No. 08/162,407 ('407) that was filed on December 3, 1993 before the Lyman *et al.* reference was published. It is asserted that on page 30, line 4 to page 31, line 33, the '407 application describes the use of flt3 ligand for hematopoietic cell culture, and flt3 ligand's stimulatory effect on pluripotent hematopoietic stem cells. This is not persuasive as there is no written description in the '407 application which suggests that applicants contemplated a hematopoietic cell expansion medium as the invention. While pharmaceutical compositions are disclosed and claimed, there is no disclosure of a hematopoietic cell expansion media. Moreover, the invention claimed in the instant application, i.e., a media composition comprising flt3-ligand and a cell growth medium, is broader in scope than the teachings in the '407 application.

It is further asserted that claim 5, drawn to hematopoietic cell expansion media contain flt3 ligand and steel factor (SF) is also supported by this disclosure because the C-*kit* expressing stem cells were purified using biotinylated SF. This argument is not persuasive as there is no description in the '407 application regarding a medium formulation comprising flt3-ligand and SF.

To overcome the 35 U.S.C. 102(a) and 103(a) rejections, it is suggested that applicants file an affidavit or declaration under 37 CFR 1.132 showing that the reference invention is not by "another", or file an affidavit or declaration under 37 CFR 1.131 showing prior invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-18, 27, and 29 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 9, and 10 of copending Application No. 08/399,404 for the reasons of record.

Applicants request that this rejection be held in abeyance until the finding of allowable subject matter is acknowledged.

Claims 2, 18 and 28 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 5,843,423 (newly applied). Claims 2, 18, and 28 are directed to a method for expanding hematopoietic cells comprising contacting the cells with flt3-ligand, alone or in combination with other growth factors, in an amount sufficient to cause expansion of the cells. As written, the methods encompass both *in vivo* and *in vitro* applications. The patented claims are directed to *in vivo* methods for expanding hematopoietic cells comprising contacting the cells with flt3-ligand, alone or in combination with other growth factors, in an amount sufficient to stimulate hematopoietic cell proliferation. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods of the instant claims, directed to expanding hematopoietic cells, requires the same process step, i.e., contacting hematopoietic cells with flt3-ligand either alone or in combination with an additional growth factor in an amount sufficient to cause hematopoietic cell expansion, and has the same end result, i.e., stimulating the proliferation of hematopoietic cells, as the patented methods.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to Deborah Clark, Supervisory Primary Examiner of Art Unit 1633, at (703) 305-4051. Any administrative or procedural questions should be directed to Kimberly Davis, Patent Analyst, at (703) 305-3015. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401.

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Patent Examiner
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MICHAEL C. WILSON
PATENT EXAMINER